REMARKS / ARGUMENTS

Claims 1, 5-16, 29-30 and 34-35 are pending and stand rejected. By the foregoing amendment, the applicants have amended claims 1, 9, 11 and 13 and canceled claim 29. Claim 36 is new. No new matter is added by the amendments. Support for the amendments are found in the specification as filed, for example on pages 6, 7 and 9. Reconsideration and allowance are respectfully requested.

On page 5 the Examiner maintained the rejection of claims 1, 5-16 and 29-30 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Pat. No. 6,991,816 (Esperester et al., the "'816 patent") in view of Struengmann (U.S. 6,284,269, "Struengmann") in view of Mathowitz (1999) in view of Esperester et al. (WO 01/28363, the "'363 reference") in view of Abramovici et al. (U.S. 6,303,626, "Abramovici") in view of Saslawski et al. (U.S. 6,426,087, "Saslawski"). Amended claims 1 and 9 are not obvious over the combined cited references.

Amended claim 1 recites, in part, a film coated tablet comprising (a) 38% to 48% by weight of at least one excipient; (b) at least 50% by weight of a dried extract, the dried extract consisting essentially of ingredients of an aqueous extract of red vine leaves and about 2.5% to about 7.5 % by weight of colloidal, anhydrous silica. The combination of the references does not result in the claimed range of colloidal, anhydrous silica.

The '816 patent teaches a composition consisting essentially of an aqueous red vine leaf extract and a pharmaceutical carrier. The '816 patent neither teaches nor suggests a dried extract comprising colloidal, anhydrous silica, let alone a tablet having the claimed range of colloidal, anhydrous silica.

The remaining references, alone or in combination, fail to cure the deficiencies of the '816 patent. Neither Mathiowitz nor Saslawski teach or suggest colloidal, anhydrous silica as part of a dried extract or as an excipient and disintegrant. The Examiner alleged that the silicon dioxide of the '363 reference is colloidal silica and is anhydrous (pages 6-7 of the Office Action). However, silicon dioxide, as described in the '363 reference, is not equivalent to the instantly claimed anhydrous colloidal silica. Specifically, anhydrous colloidal silica is characterized by a specialized preparation process resulting in a "light, fine, white, amorphous powder, with a particle size of about 15 nm" (see page 2410 of the European Pharmacopoeia 5.0,

a copy attached for the Examiner's convenience). The '363 reference merely mentions that silicon dioxide (not colloidal, anhydrous silica) may be added as a carrier or excipient in order to facilitate processing and not to enhance stability (pages 4-5 of the '363 reference). Therefore, the '363 reference does not teach or suggest colloidal, anhydrous silica.

Struengmann and Abramovici disclose colloidal, anhydrous silica. However, Struengmann merely mentions colloidal, anhydrous silica may be used as a tablet additive. There is no teaching or suggestion in Struengmann to employ a dried extract consisting essentially of leaves and about 2.5% to about 7.5% by weight of colloidal, anhydrous silica produced in a drying process comprising the steps of adding colloidal, anhydrous silica during the drying process. Abramovici discloses a tablet comprising only 2% colloidal, anhydrous silica. Neither Struengmann nor Abramovici teach or suggest the claimed amount of colloidal, anhydrous silica, let alone colloidal, anhydrous silica as part of a dried extract. At most, the combination of the references results in a tablet having 2% colloidal, anhydrous silica as an additive. The combination of the cited references cannot result in the subject matter of amended claim 1, a tablet having a dried extract containing about 2.5% to about 7.5% by weight of colloidal, anhydrous silica. Nor can the combination of the cited references result in the subject matter of amended claim 9, i.e., a tablet according to claim 1 further having an excipient which can include the disintegrant colloidal, anhydrous silica.

In view of the foregoing, the combination of the cited references cannot result in the claimed subject matter. Therefore, claims 1, 5-16 and 30 are non-obvious over the cited references and are thus allowable. Accordingly, the applicants request the Examiner withdraw this rejection.

On page 11 the Examiner maintained the rejection of claims 1, 5-16 and 29-30 and newly rejected claims 34-35 under 35 U.S.C. § 103(a) as being unpatentable over Esperester et al. (WO 01/28363, the "'363 reference") in view of Bilgrami et al. (1993) in view of Struengmann in view of Mathiowitz in view of Saslawski et al. in view of Abramovici et al. and in view of Lieberman, H., Ed. et al. (1990). Amended claim 1 is recited above. For reasons similar to those discussed above, the combination of the references does not teach or suggest amended claim 1.

The deficiencies of the '363 reference are discussed above. The remaining references, alone or in combination, fail to cure the deficiencies of the '363 reference. The shortcomings of

Struengmann and Abramovici are discussed above. None of Bilgrami, Mathiowitz, Saslawski and Lieberman teach or suggest colloidal, anhydrous silica as part of a dried extract. Thus, the combination of the references cannot result in the instantly claimed invention and therefore, claims 1, 5-16, 30 and 34-35 are non-obvious over the cited references.

Additionally, the Examiner did not find persuasive the arguments previously submitted in the Response of January 26, 2010. By way of background, the applicants previously submitted data in the Esperester Declaration submitted September 25, 2008, showing that superior storage stability characteristics, i.e., stability against moisture, air and temperature, occurred in the applicant's tablets where the colloidal, anhydrous silica was added to the red vine leaf extract **during** the spray drying process. The Examiner contends (1) that the improved flow properties, reduced tablet thickness and improved tablet hardness resulting from the addition of colloidal silica of Chang is "related to disintegration as are extrinsic parameters such as moisture, air and temperature" (page 26 of the Office Action); (2) that the Esperester Declaration does not provide any evidence of an unexpected result in view of the relatedness of the characteristics of Chang to the superior stability characteristics of the claimed tablets (page 27 of the Office Action); (3) that the tablets in the Esperester Declaration are too different to merit a true comparison (page 28 of the Office Action); and (4) the Applicants have not explained the very large "discrepancy of crospovidone between the tested formulations in the Esperester Declaration did not attribute to the disintegration rate of the formulation" (page 29 of the Office Action). The applicants address each contention below.

Regarding contentions (1) and (2), the applicants disagree and note the Examiner has incorrectly interpreted the teachings of Chang. Chang explicitly states "that powder mixtures containing up to 1% colloidal silica generally resulted in a decrease in the tensile strength" and "the presence of lubricants and glidants in the formulation will generally produce weak bonding" (*see* introduction and first paragraph of the results and discussion of Chang). The increased tablet crushing strength cited by the Examiner is the exception rather than a general rule. Chang specifies that this effect is only observed "in some cases" (*see* first paragraph of the results and discussion of Chang). Specifically, all of the cases described in Chang were observed only when colloidal silica was combined with DMP 504. A skilled artisan viewing Chang would not contemplate that combining 2.5% colloidal, anhydrous silica with an active ingredient other than

DMP 504 would result in an increase in tablet crushing strength, let alone any superior storage stability characteristics.

Furthermore, Chang does not disclose colloidal silicon dioxide concentrations of greater than 2% of the total mixture. Chang teaches the use of only "a small amount of colloidal silicon dioxide" (2% or less as described in Figure 4 of Chang) otherwise "addition of colloidal silica above the precise concentration range results in a decreased flow and a loss of cohesion in the tablet" (*see* first paragraph of the introduction and the last paragraph of the results and discussion of Chang). Clearly, Chang does not contemplate a colloidal silicon dioxide concentration higher than 2% of the total mixture. A skilled artisan viewing Chang would not contemplate using colloidal silicon dioxide at the levels claimed in amended claim 1. In fact, Chang clearly teaches increasing the amount of colloidal silica would have detrimental effects (reduced crushing strength).

Regarding contention (3), the Examiner points to the different amounts of colloidal anhydrous silica in Formulation I (4 mg) and Formulation II (6 mg). As previously discussed in the Response submitted January 26, 2010, the applicants submitted that the 2 mg difference in the solution prior to spray drying is not significant in light of the additional 15 mg of colloidal anhydrous silica added to the red vine extract of Formulation II **during** the drying step. As discussed above, the addition of colloidal anhydrous silica during the drying step of the red vine leaf extract unexpectedly resulted in superior storage stability properties of the resulting spray-dried powder. One skilled in the art would not expect the small difference in the amount of silica in the solution to affect the more than 7-fold increase in silica added during the drying step. Therefore, a skilled artisan would reasonably conclude that a comparison between Formulation I and Formulation II is valid.

Regarding contention (4), the applicants submit that a disintegrant (such as crospovidone, which is a well-known hygroscopic disintegrant) does not enhance the storage stability of a tablet but rather, as is well-known, increases the disintegration rate thereby reducing storage stability. Hence, the expected effect of crospovidone in Formulation II on the disintegration rate would be an increase of the disintegration rate (and therefore a reduced storage stability) over that of Formulation I which lacks any crospovidone. However, the opposite effect was observed in the data of the Esperester Declaration. The superior storage stability observed in Formulation II

having both colloidal anhydrous silica and the additional disintegrant (crospovidone) as compared to Formulation I was unexpected as one skilled in the art would reasonably conclude that the crospovidone of Formulation II would contribute to reducing storage stability. In fact, it would be reasonable to conclude that the difference in storage stability between Formulations I and II would have been even greater if crospovidone had not been present in Formulation II. Therefore, the discrepancy between the amount of crospovidone in the formulations does not affect the validity of comparing Formulation I to Formulation II in determining superior storage stability characteristics.

In light of the above discussion, the applicants submit the superior effects of the claimed subject matter are clearly illustrated by the data submitted in the Esperester Declaration. The data clearly shows that the unexpected superior storage stability characteristics naturally result from the claimed invention and may be used to show nonobviousness (*In re Zenitz*, 333 F.2d 924, 142 USPQ 158 (C.C.P.A. 1964)). It would not have been obvious to combine the references given the unexpected benefits resulting from the addition of about 2.5 to about 7.5% by of colloidal, anhydrous silica to the aqueous extract of red vine leaves during the drying process. In light of the unexpected results, claims 1, 5-16, 30 and 34-35 are non-obvious and allowable. Accordingly, the applicants request the Examiner withdraw this rejection.

Applicants submit that all claims pending in the patent application are in condition for allowance. Accordingly, both reconsideration of this application and its swift passage to issuance are earnestly solicited. The fee for a one-month extension is included herewith. In the event there are any fees due and owing in connection with this matter, please charge same to our Deposit Account No. 11-0223.

Respectfully submitted,

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